

CHAPTER 23

Fever

Alan R. Roth and Gina M. Basello

Fever is one of the most common presenting complaints encountered by the family physician during acute office visits in the United States. Fever is generally defined as a temperature higher than 38.3° C (100.9° F). Most cases of fever are secondary to acute viral illnesses and are generally termed upper respiratory infections (URIs). Other common causes of fever include viruses such as GI and influenza, sinusitis, pharyngitis, bronchitis, pneumonia, and urinary tract infections (UTIs).

A careful history and problem-focused physical examination is essential to the accurate diagnosis and management of these conditions. A cost-effective evidence-based approach to the diagnosis and management of febrile illness, including the appropriate use of antibiotic therapy, is the cornerstone of quality medical care.

MEDICATION CAUSES OF FEVER

Fever secondary to many medications is a common cause of prolonged fever or fever of undetermined origin in the adult and pediatric patient. This etiology of fever should be considered in all patients who are taking medications of any kind. If the initial evaluation of a patient fails to reveal a source of the temperature, or if infectious or other etiologies seem unlikely, then medication causes of fever should be considered. Typically fever presents within the first 7 to 10 days of medication use; however, the presentation may be variable and can present even years after initiation of medication.

Symptoms

- Fever +++++
- Chills or rigors +++
- A sense of well-being +++

Signs

- Usually normal physical examination ++++
- Morbilliform rashes ++

Workup

- The workup should include a thorough history and physical examination. Most patients with drug-induced fever appear well with an absence of physical findings.

- A detailed history of medication use that includes any prescription or nonprescription medications, vitamins, and other herbal agents should be taken.
- Routine laboratory testing including a CBC may reveal the presence of eosinophilia.
- Although any agent may produce a medication-induced fever, the most common agents include antibiotics, antihypertensives, CNS and cardiovascular agents, heparin, and analgesics.

Comments and Treatment Considerations

If the initial evaluation of any patient who presents with a fever fails to reveal an underlying etiology, drug fever should be suspected.

In any patient who presents with a fever 7 to 10 days after starting a new medication, drug fever should be ruled out before beginning any extensive diagnostic evaluation.

A diagnosis of medication-induced fever can only be made if resolution of the fever occurs within 48 hours or three to five half-lives of the drug after discontinuation.

Drug fever may sometimes be associated with serum sickness-like reactions. These patients are usually much sicker and often present with erythema multiforme or exfoliative dermatitis. Resolution of symptoms in these patients is much slower and treatment is symptomatic.

PNEUMONIA

Community-acquired pneumonia (CAP) is the most common of all pneumonias and is a common etiology of febrile illness. The most common include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and atypical organisms such as mycoplasma, legionella, and influenza. Patients usually present with fever, chills, cough, pleuritic chest pain, and dyspnea. An accurate assessment of the patient is essential in determining the need for hospitalization and appropriate antibiotic selection. The use of evidence-based clinical pathways and consensus guidelines is important for accurate diagnosis and cost-effective management.

Symptoms

- Fever, chills, rigors, generalized malaise ++++
- Dyspnea +++
- Pleuritic chest pain ++
- Cough: dry or productive, colored (green-yellow or rust) sputum ++++
- Hemoptysis ++
- Atypical pneumonias may be associated with generalized constitutional and GI symptoms. ++++

Signs

- Fever +++
- Tachypnea and tachycardia +++
- Crackles or rales +++

- Dullness to percussion ++
- Bronchial breath sounds ++
- Tactile fremitus ++

Workup

- Chest radiography (posteroanterior and lateral views) are essential in making a diagnosis of pneumonia. Typical pneumonias present with a lobar consolidation, whereas atypical pneumonia presents with more bilateral and diffuse infiltrates. Chest radiography is also important to rule out complications of pneumonia such as pleural effusion, multilobar disease, and abscess. All infiltrates should be followed until complete resolution. Underlying pulmonary or neoplastic diseases cannot be excluded before 8 to 12 weeks.
- A leukocytosis count ranging between 15,000 and 25,000 cells/ μ L with increased immature cells is most often seen.
- Sputum Gram stain should be performed but its usefulness is controversial. Contamination, limited sensitivity and atypical organisms limit the benefits of the test.
- Blood cultures (two sets) may be obtained on all patients who require hospitalization but rarely affects treatment. The use of blood cultures in the ambulatory setting is limited and not considered necessary or cost-effective.
- Urinary antigens and PCR testing for common pathogens are important in the diagnosis and management of the critically ill patient.
- Additional testing of the hospitalized patient should include electrolytes, liver function studies, and arterial blood gases.

Comments and Treatment Considerations

Initial treatment of pneumonia is empiric and should be based on a careful history, physical examination, preliminary workup, and patient risk stratification. Following published consensus guidelines from the American Thoracic Society or the Infectious Disease Society of America will guide appropriate antibiotic selection.

The decision to treat a patient in the outpatient setting or admit to the hospital should be based on clinical judgment and the use of clinical pathways such as the pneumonia severity index. Increased risk is associated with factors including age, comorbid illness, smoking history, findings on physical examination, and laboratory workup.

Treatment of CAP should be initiated empirically with the use of antibiotics that will cover streptococcal pneumonia and atypical pathogens. Acceptable first-line agents include macrolides, fluoroquinolones, and doxycycline.

The emergence of increasing resistance of *S. pneumoniae* is of great concern. The prevalence of penicillin-resistant strains of *S. pneumoniae* is as high as 25%. Significant resistance is also seen with macrolides, fluoroquinolones, cephalosporins, and other agents.

Controversy exists and the working group of the CDC recommends limiting the initial use of fluoroquinolones because of concerns of emerging resistance that have occurred following the liberal use of these agents. The CDC recommends that these agents be reserved

for second-line therapy or in patients with significant comorbidities. They recommend starting therapy with a macrolide, doxycycline, or an oral β -lactam.

Hospitalized patients should be risk stratified for potential admission to an intensive care unit. Empirical antibiotic therapy should be started with a β -lactam plus macrolide or a fluoroquinolone. Broad-spectrum therapy may be indicated in patients who are from nursing homes, are immunocompromised, have significant comorbidities, or develop hospital-acquired pneumonia. Further therapy should be guided by results of the initial evaluation and patient response to therapy.

Adjunctive therapies may include antipyretics, expectorants and cough suppressants, and oxygen and bronchodilator therapy. The use of circulatory and respiratory support may be necessary in the critically ill patient.

Because of the changing microbiology of pneumonia, clinicians should periodically confirm updated treatment recommendations.

PYELONEPHRITIS

Pyelonephritis is a common cause of febrile illness in both adults and children. Acute pyelonephritis is defined as an uncomplicated infection of the upper urinary tract. More than 100,000 hospitalizations annually are secondary to infections related to the urinary tract. The condition is much more common in women, who are five times more likely than men to require hospitalization. In men, underlying causes such as benign prostatic hypertrophy, prostatitis, or nephrolithiasis are usually evident. *Escherichia coli* accounts for more than 80% of cases of acute pyelonephritis. Other common pathogens include gram-negative bacteria, *Staphylococcus saprophyticus*, and enterococci. Early use of effective antibiotics is essential in reducing morbidity and unnecessary hospitalizations.

Symptoms

- Fever +++++
- Chills +++++
- Nausea and vomiting +++++
- Diarrhea ++
- Back pain +++++
- Suprapubic or abdominal pain ++
- Gross hematuria ++
- Dysuria, urinary frequency and urgency +++

Signs

- Tachycardia, diaphoresis +++
- Costovertebral angle tenderness that may be unilateral or bilateral +++++
- Lower abdominal or suprapubic tenderness and guarding +++
- In older adults, fever and other common symptoms of urinary tract infection may be absent. GI symptoms are most frequently seen. +++

Workup

- Urinalysis is effective using the dipstick method to detect leukocyte esterase or nitrate. Microscopic analysis for WBCs, RBCs, WBC casts, and bacteria is also useful.
- Urine culture and sensitivity should be performed on all patients with a differential diagnosis that includes pyelonephritis. Urine cultures are positive in more than 90% of patients with pyelonephritis. A urine culture is considered positive if it reveals greater than 10,000 colony-forming units (CFUs) and symptoms compatible with pyelonephritis, whereas in uncomplicated cystitis, counts of 50 to 100,000 CFUs are considered positive. Lower numbers should be carefully evaluated in males, and in immunocompromised or pregnant patients. Urine cultures are not necessary in uncomplicated cases of nonfebrile cystitis in the ambulatory setting.
- Blood culture and sensitivity is recommended only for hospitalized patients and yields are very low.
- Imaging studies including, ultrasonography, IV pyelography, CT scanning, and MRI may be indicated to rule out underlying anatomic abnormalities, nephrolithiasis, complications and other coexisting conditions as well as to confirm the diagnosis.
- Hospitalized patients should also receive a CBC and electrolytes to monitor systemic effects of infection and renal function.

Comments and Treatment Considerations

Most patients with acute pyelonephritis can be treated in the ambulatory setting. Indications for admission include the very young, older adults, diabetic or other immunocompromised patients, intractable vomiting or inability to tolerate oral intake, toxic-appearing patients, or those with progression of uncomplicated infections.

Most consensus guidelines recommend fluoroquinolones as empiric first-line antimicrobial therapy. Resistance to fluoroquinolones by common pathogens of the urinary tract is increasing. Orally administered ciprofloxacin is considered the drug of choice for uncomplicated infections in nonpregnant individuals. Alternative treatment options include amoxicillin-clavulanate potassium and cephalosporins, particularly with fluoroquinolone resistance.

Patients who require hospitalization should be treated with a fluoroquinolone if hospital resistance rates are low, an aminoglycoside with ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside.

Most patients should be treated for a total of 10 to 14 days. Short regimens of 3 to 5 days are only indicated for cases of uncomplicated cystitis.

Fluoroquinolones are classified as a pregnancy Category C drug and should not be used in pregnant women because of possible teratogenic effects on the fetus. Amoxicillin and amoxicillin-clavulanate potassium are considered agents of choice in pregnant women. All pregnant women who present with pyelonephritis should be hospitalized for IV hydration and antibiotics.

Complications include septicemia, chronic pyelonephritis, hydro-nephrosis, perinephric abscess formation, hypertension, and renal failure.

Treatment failures are usually secondary to resistant organisms, nephrolithiasis, or underlying anatomic abnormalities.

UPPER RESPIRATORY INFECTION

URIs account for almost 50 million visits to primary care physicians each year. Viral infections such as the common cold account for the vast majority of these infections. More than 150 million prescriptions for antibiotics are written for these conditions on an annual basis, many of which are not justified. A careful evidence-based approach using clinical practice guidelines and consensus recommendations is essential for a rational approach to the diagnosis and management of these conditions. A problem-focused history and physical examination will guide the determination of a specific diagnosis that may require targeted antibiotic therapy. The differential diagnosis of these conditions includes pharyngitis, tonsillitis, otitis media, and sinusitis as well as complications such as abscess formation and disseminated infections.

Symptoms

- Sore throat +++
- Fever +++
- Cough +++
- Nasal congestion, rhinorrhea, sneezing, or postnasal drip +++++
- Headache, facial or dental pain ++
- Pain or fullness in the ear ++
- Systemic symptoms such as nausea, vomiting, or diarrhea ++

Signs

- Erythema of the oropharynx, tonsillar hypertrophy, and/or exudates +++
- Cervical lymphadenopathy +++
- Abdominal tenderness and/or hepatosplenomegaly ++
- Clear or purulent nasal discharge +++++
- Sinus tenderness ++
- Fullness or bulging of the tympanic membrane with distinct erythema and air-fluid levels ++

Workup

- A careful and problem-focused history and physical examination is the key to accurate diagnosis.
- Acute pharyngitis is most often secondary to viral pathogens. The presence of tonsillar erythema, exudates, and anterior cervical lymphadenopathy raises the suspicion for group A beta-hemolytic streptococcus (GABHS) infection. Predicting which patients have GABHS infection is essential. Using a clinical scale such as the McIsaac Prediction System can allow for a treatment decision in

many cases without laboratory tests. In equivocal cases, rapid antigen detection tests with culture may help guide appropriate therapy.

- If concern for mononucleosis is present or if symptoms persist, a diagnosis of infectious mononucleosis should be considered. A CBC revealing the presence of atypical lymphocytes and a positive heterophile test will confirm the diagnosis.
- AOM manifests as an acute onset febrile illness with localized symptoms of ear pain. Mobility of the tympanic membrane should be evaluated with the use of pneumatic otoscopy, tympanometry, or acoustic reflectometry.
- Acute rhinosinusitis is a clinical diagnosis that is made when symptoms of an acute URI do not remit after 7 to 10 days. Purulent nasal discharge and unilateral pain are the typical symptoms most predictive of acute sinusitis. The use of CT scanning can be used to diagnose difficult cases or help with management decisions in persistent cases.

Comments and Treatment Considerations

Most cases of URIs can be treated with watchful waiting along with symptomatic treatment such as antipyretics, analgesics, antihistamines, decongestants, nasal saline sprays, expectorants, and cough suppressants.

GABHS infection should be treated with antimicrobial therapy. The use of oral penicillin four times daily for 10 days remains the treatment of choice. Some clinicians prefer amoxicillin due to the better taste and dosing schedule. Macrolides such as clarithromycin or azithromycin can be used in patients with penicillin allergy. Studies have shown that 5-day courses of advanced-generation cephalosporins or macrolides are effective therapy.

Documented cases of acute otitis media and sinusitis may be treated with antimicrobial therapy aimed at the most common organisms including *S. pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis*. First-line therapy remains amoxicillin. Alternative therapy in very ill or nonresponsive cases includes amoxicillin-clavulanate, advanced-generation cephalosporins, or macrolides, and sulfa-based combinations. Adults may be treated with doxycycline or advanced generation fluoroquinolones, but their use should be limited due to the emergence of resistance. Careful follow-up should be arranged with patients with unusual sinus infections such as frontal and ethmoid sinusitis because serious complications may be seen. Adjunctive therapy should include analgesic and antipyretic medications. The use of nasal saline and inhaled steroids may be effective in the treatment of sinusitis.

VIRAL SYNDROME

Viral infections are the underlying etiology in most patients who present with febrile illness. Common viral infections include upper and lower respiratory tract infections including the “common cold,” gastroenteritis, and influenza. Diagnosis of most viral infections

is based on the clinical presentation, physical examination, and the exclusion of bacterial etiologies. Knowledge of the common outbreaks and pathogens of the local community is helpful in the diagnosis of viral infections. Rapid-antigen testing is becoming increasingly available and cost-effective in the management of the patient with “viral illnesses.” The use of consensus recommendations and clinical practice guidelines, including the judicious use of antibiotics for patients only with clearly documented bacterial infection, is important in the prevention of emerging resistant bacterial pathogens.

Symptoms

- Fever and chills +++++
- Fatigue and weakness ++++
- Coryza +++
- Sneezing, congestion, sore throat +++
- Headache ++
- Myalgia, arthralgia ++
- Anorexia, nausea, vomiting, and diarrhea ++
- Rashes ++

Signs

- Absence of toxic-appearing clinical features +++
- Diaphoresis ++
- Tachycardia ++
- A physical examination that does not reveal the presence of other etiologies such as acute otitis media, sinusitis, pneumonia, or pyelonephritis +++++

Workup

- The initial approach to the patient with fever should include a careful history, physical examination, and appropriate laboratory testing.
- Patients who are very ill or toxic appearing should have a laboratory workup. Admission to the hospital should be based mainly on clinical judgment.
- First-line testing should include a CBC. An increase in lymphocytes in the differential suggests a viral etiology for the condition.
- Serum electrolytes are indicated in the presence of possible dehydration.
- Liver function studies may be helpful but are nonspecific findings if elevated and may require the use of additional studies for the presence of acute hepatitis.
- Blood culture and sensitivity (two sets) to rule out bacterial pathogens is indicated in the acutely ill or toxic-appearing patient.
- Urinalysis and culture is indicated in the evaluation of a patient with a possible asymptomatic UTI, which occurs especially in infants and older adults.
- Chest radiography may be indicated in the presence of adventitious sounds on auscultation.

- Additional studies may include nasopharyngeal cultures, throat cultures, stool cultures, and rapid antigen testing. Rapid antigen testing is readily available for the diagnosis of common viral pathogens such as influenza A and B or rotavirus infections.

Comments and Treatment Considerations

A careful history and physical examination are essential for the accurate diagnosis of viral infections as well the exclusion of bacterial pathogens that may require antimicrobial therapy.

Close monitoring of local community or hospital pathogen prevalence data is important to aid in diagnosis, guide appropriate therapy, and prevent the outbreak of disease.

Prevention using handwashing, isolation of infected individuals, vaccination of appropriate individuals, and use of prophylactic antiviral agents is important in decreasing morbidity and mortality.

Amantadine and rimantadine are antiviral agents indicated for the prophylaxis and treatment of influenza virus. The agents are inexpensive but are only effective against influenza A and resistance is high. The agents must be given within 48 hours of symptoms to be effective.

Oseltamivir is a neuraminidase inhibitor indicated for the treatment of influenza A or B in patients more than 1 year of age within the first 48 hours of symptoms. The drug is administered orally. The drug may also be used for prophylaxis in individuals older than the age of 13. Studies show that the medication may reduce the duration of symptoms by up to one and one half days as well as decrease the morbidity and mortality associated with the disease.

Symptomatic therapy of all patients should include antipyretics, analgesics, antidiarrheal agents, and cough and cold medications as indicated. Adequate hydration is essential in maintaining fluid volume and preventing hospitalization.

Antibiotics should be used only in those patients who develop secondary bacterial infections.

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